

(d) detecting the label.

100. The method of claim 99, wherein said fluorescent label is a chromogen.

101. The method of claim 100, wherein said chromogen is a fluorochrome.

102. The method of claim 99, further comprising the step of removing lesions at sites of elevated label accretion with laser therapy, brachytherapy, chemoimmunotherapy, radioimmunotherapy, photodynamic therapy, external beam irradiation or surgical removal.

103. The method of claim 102, further comprising the step of treating lesions at sites of elevated label accretion with ionizing radiation.

104. The method of claim 100, wherein the procedure is selected from the group consisting of an endoscope, laparoscope, and intravascular catheter procedures, further comprising the step of administering brachytherapy via an endoscope or catheter to lesions at sites of elevated label accretion.

105. The method of claim 99, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

106. The method of claim 99, wherein the fragment or subfragment is monospecific.

107. The method of claim 99, wherein the fragment or subfragment is bispecific.

108. The method of claim 99, wherein the fragment or subfragment has a molecular weight of 65,000 daltons or less.

109. The method of claim 99, wherein the fragment or subfragment has a molecular weight of 55,000 daltons or less.

110. The method of claim 99, wherein the fragment or subfragment has a molecular weight of 50,000 daltons or less.

111. The method of claim 99, wherein said procedure is conducted within 24 hours of the injection of said labeled antibody fragment or subfragment.

112. The method of claim 99, wherein said procedure is a laparoscopic procedure.

113. The method of claim 99, wherein the label is detected without the use of a clearing agent, contrast agent or subtraction agent.

114. The method of claim 99, wherein the procedure is an operative procedure.

115. A method of detection and treatment of lesions during an operative, endoscopic, laparoscopic, or intravascular catheter procedure, wherein the method comprises:

A (a) injecting a patient to undergo such a procedure with a divalent single chain antibody fragment or subfragment with a molecular weight of 85,000 Daltons or less, labeled with an agent capable of detection, which labeled antibody fragment or subfragment preferentially accretes at the lesion;

(b) permitting the labeled antibody fragment or subfragment to accrete at the lesion;

(c) conducting the procedure within 48 hours of the injection;

(d) detecting the agent; and

(e) treating the lesion by brachytherapy administered through the endoscope or intravascular catheter.

116. The method of claim 115, wherein the patient is injected with a first composition comprising a streptavidin- or avidin-conjugated protein, biotinylated protein to be used in conjunction with avidin and biotin, bifunctional protein, protein-hapten complex, or enzyme conjugated protein, wherein said protein specifically accretes at the targeted lesion; and after the first composition accretes at the targeted lesion, the patient is injected with a second composition, wherein said second composition bears a labeling agent capable of detection and which couples with the first composition.

117. The method of claim 116, wherein said first composition comprises a biotinylated protein, said second composition comprises a biotin conjugated with a labeling agent, and wherein after the first agent accretes at the targeted lesion but prior to injecting said second composition, the patient is injected with a clearing composition comprising an agent to clear circulating biotinylated protein.

118. The method of claim 117, wherein said clearing composition comprises a galactosylated anti-idiotypic clearing agent.

119. The method of claim 115, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

120. The method of claim 115, wherein the fragment or subfragment is monospecific.

121. The method of claim 115, wherein the fragment or subfragment is bispecific.

122. The method of claim 115, wherein the fragment or subfragment has a molecular weight of 65,000 daltons or less.

123. The method of claim 115, wherein the fragment or subfragment has a molecular weight of 55,000 daltons or less.

124. The method of claim 115, wherein the fragment or subfragment has a molecular weight of 50,000 daltons or less.

125. The method of claim 115, wherein said procedure is conducted within 24 hours of the injection of said labeled antibody fragment or subfragment

126. The method of claim 115, wherein said procedure is a laparoscopic procedure.

127. The method of claim 115, wherein the label is detected without the use of a clearing agent, contrast agent or subtraction agent.

128. The method of claim 115, wherein the procedure is an operative procedure.

129. The method of claim 115, wherein said fragment or subfragment is labeled with a diagnostic radio isotope or a MRI image enhancing agent.

130. The method of claim 129, wherein said MRI enhancing agent is a paramagnetic metal.

131. The method of claim 130, wherein said paramagnetic metal is Mn or Gd.

132. The method of claim 129, wherein said diagnostic radioisotope is selected from the group consisting of a gamma, beta and positron emitter.

133. The method of claim 129, wherein said diagnostic radioisotope has an energy between 20 to 1000 keV.

134. A method of treatment of lesions during a laparoscopic or intravascular catheter procedure, wherein the method comprises:

(a) injecting a patient to undergo such a procedure with a divalent single chain antibody fragment or subfragment with a molecular weight of 85,000 Daltons or less, labeled with a photoactive agent, wherein the antibody fragment or subfragment preferentially accretes at targeted lesions;

(b) permitting the labeled antibody fragment or subfragment to accrete;

(c) conducting the procedure within 48 hours of the injection; and

activating the photoactive agent with a light source, thereby treating said lesions.

135. The method of claim 134, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

136. The method of claim 134, wherein the fragment or subfragment is monospecific.

137. The method of claim 134, wherein the fragment or subfragment is bispecific.

138. The method of claim 134, wherein the fragment or subfragment has a molecular weight of 65,000 daltons or less.

139. The method of claim 134, wherein the fragment or subfragment has a molecular weight of 55,000 daltons or less.

140. The method of claim 134, wherein the fragment or subfragment has a molecular weight of 50,000 daltons or less.

141. The method of claim 134, wherein said procedure is conducted within 24 hours of the injection of said labeled antibody fragment or subfragment.

142. The method of claim 134, wherein said procedure is a laparoscopic procedure.

143. The method of claim 134, wherein the procedure is an operative procedure.

144. A method of treatment of lesions, wherein the method comprises:

(a) injecting a patient with composition comprising a divalent single chain antibody fragment or subfragment with a molecular weight of 85,000 Daltons or less, conjugated to an agent capable of being activated to emit Auger electrons or other ionizing radiation, and, optionally, to an agent capable of detection, wherein the antibody conjugate accretes preferentially at the targeted lesion; and

(b) activating said agent capable of being activated, thereby treating said lesions, and, optionally, detecting the optional agent capable of detection.

145. The method of claim 144, wherein the activation and optional detection is during an endoscopic, intravascular, catheter or surgical procedure.

146. The method of claim 144, wherein said procedure is a laparoscopic procedure.

147. The method of claim 144, wherein the activatable agent is a stable element capable of being activated to emit ionizing radiation.

148. The method of claim 144, wherein the activatable agent is a stable element capable of being activated to emit Auger electrons.

149. The method of claim 144, wherein the activatable agent is a halogenated compound.

150. The method of claim 149, wherein the agent is a halogenated pyrimidine.

151. The method of claim 147, wherein the stable element is iodine or indium.

152. The method of claim 144, wherein the activating energy is monochromatic X-rays.

153. The method of claim 152, wherein the monochromatic X-rays emit at an energy of 20-70 keV.

154. The method of claim 153, wherein the monochromatic X-rays emit at an energy of 30-40 keV.

155. The method of claim 144, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

156. The method of claim 144, wherein the fragment or subfragment is monospecific.

157. The method of claim 144, wherein the fragment or subfragment is bispecific.

158. The method of claim 144, wherein the fragment or subfragment has a molecular weight of 65,000 daltons or less.

159. The method of claim 144, wherein the fragment or subfragment has a molecular weight of 55,000 daltons or less.

160. The method of claim 144, wherein the fragment or subfragment has a molecular weight of 50,000 daltons or less.

161. The method of claim 144, wherein the procedure is an operative procedure.

162. A method of obtaining biopsy samples, wherein the method comprises:

(a) injecting a patient subject to such a procedure parenterally with an effective amount of a labeled antibody fragment or subfragment, which specifically binds an antigen produced by or associated with a lesion;

(b) probing and scanning the accessed interior of the patient at close range with a detection means for detecting the presence of the labeled antibody fragment or subfragment;

(c) locating the sites of accretion of the labeled antibody fragment or subfragment by detecting elevated levels of the labeled antibody fragment or subfragment at such sites; and

(d) inserting a biopsy implement into one or more sites of elevated accretion to obtain a biopsy sample, wherein said locating and said biopsy are conducted within 48 hours of the injection.

163. The method of claim 162, wherein the patient is injected with a first composition comprising a streptavidin- or avidin-conjugated protein, biotinylated protein to be used in conjunction with avidin and biotin, bifunctional protein, protein-hapten complex, or enzyme conjugated protein, wherein said protein specifically accretes at the targeted lesion; and after the first composition accretes at the targeted lesion, the patient is injected with a second composition, wherein said second composition bears a labeling agent capable of detection and which couples with the first composition;

164. The method of claim 163, wherein said first composition comprises a biotinylated protein, said second composition comprises a biotin conjugated with a labeling agent, and wherein after the first agent accretes at the targeted lesion but prior to injecting said second composition, the patient is injected with a clearing composition comprising an agent to clear circulating biotinylated protein.

165. The method of claim 164, wherein said clearing composition comprises a galactosylated anti-idiotypic clearing agent.

166. The method of claim 162, wherein the procedure is conducted within 24 hours of the injection.

167. The method of claim 162, wherein the procedure is conducted within 12 hours of the injection.

168. The method of claim 162, wherein the procedure is conducted within 6 hours of the injection.

169. The method of claim 162, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

170. The method of claim 162, wherein the fragment or subfragment is a monoclonal antibody fragment or subfragment.

171. The method of claim 162, wherein the fragment or subfragment is monovalent and selected from the group consisting of an Fv, a single chain antibody, Fab and Fab'.

172. The method of claim 162, wherein the fragment or subfragment is a divalent single chain antibody fragment or subfragment with a molecular weight of 85,000 daltons or less.

173. The method of claim 162, wherein the fragment or subfragment is bispecific.

174. The method of claim 162, wherein the fragment or subfragment has a molecular weight of 65,000 daltons or less.

175. The method of claim 174, wherein the fragment or subfragment has a molecular weight of 55,000 daltons or less.

176. The method of claim 174, wherein the fragment or subfragment has a molecular weight of 50,000 daltons or less.

177. The method of claim 162, wherein the label for the fragment or subfragment is a radioisotope.

178. The method of claim 177, wherein the radioisotope is selected from the group consisting of technetium-99m, iodine-125, iodine-131, iodine-123, indium-111, and gallium-67.

179. The method of claim 162, wherein the label of said labeled antibody fragment or subfragment is a non-isotopic agent.

180. The method of claim 179, wherein the non-isotopic agent is a photoactive agent.

181. The method of claim 180, wherein the photoactive agent is a fluorescent agent.

182. The method of claim 162, wherein the location of sites of accretion is performed without the use of a clearing agent, contrast agent or subtraction agent.

183. A method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:



(a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less, wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;

(b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and

*A* (c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure, wherein said detection is performed without the use of a contrast agent or subtraction agent.

184. The method of claim 183, further comprising the step of injecting said patient with a clearing composition comprising an agent to clear circulating said bispecific antibody.

185. The method of claim 184, wherein said clearing composition comprises an anti-idiotypic antibody.

186. The method of claim 185, wherein said anti-idiotypic antibody is conjugated to a galactosyl residue.

187. The method of claim 183, wherein said antigen produced or associated with a lesion is a tumor- or pathogen-associated antigen.

188. The method of claim 183, further comprising the step of removing lesions at sites of elevated label accretion with a laser therapy, brachytherapy, chemoimmunotherapy, radioimmunotherapy, photodynamic therapy, external beam irradiation or surgical removal..

189. The method of claim 183, further comprising the step of treating lesions at sites of elevated label accretion with ionizing radiation.

190. The method of claim 183, wherein the procedure is selected from the group consisting of an endoscope, laparoscope, and intravascular catheter procedures, further

comprising the step of administering brachytherapy via the endoscope or catheter to lesions at sites of elevated label accretion.

191. The method of claim 183, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

192. The method of claim 183, wherein said procedure is a laparoscopic procedure.

193. The method of claim 183, wherein said hapten is labeled with a diagnostic radioisotope, a MRI image enhancing agent or a fluorescent label.

194. The method of claim 193, wherein said MRI image enhancing agent is a paramagnetic metal.

195. The method of claim 193, wherein said paramagnetic metal is Mn or Gd.

196. The method of claim 193, wherein the label of said diagnostic radioisotope is a gamma, beta or positron emitter.

197. The method of claim 196, wherein diagnostic radioisotope has an energy of 20-1,000 keV.

198. A method of detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:

(a) injecting a patient to undergo such a procedure with a first composition comprising a divalent single chain antibody fragment or subfragment with a molecular weight of 85,000 Daltons or less and labeled with an agent, wherein the labeled antibody fragment or subfragment is a streptavidin- or avidin-conjugated protein, biotinylated protein to be used in conjunction with avidin and biotin, bifunctional protein, protein-hapten complex, or enzyme conjugated protein, and wherein the protein specifically accretes at the targeted lesion;

(b) injecting a second composition after the first composition accretes at the targeted lesion, wherein said second composition bears a labeling agent capable of detection and which couples with the first composition;

(c) conducting the procedure within 48 hours of the injection; and

(d) detecting the label.

199. The method of claim 198, wherein said first composition comprises a biotinylated protein, said second composition comprises a biotin conjugated with a labeling agent, and wherein after the first agent accretes at the targeted lesion but prior to injecting said second composition, the patient is injected with a clearing composition comprising an agent to clear circulating biotinylated protein.

200. The method of claim 199, wherein said clearing composition comprises a galactosylated anti-idiotypic clearing agent.

201. An improved method for detection of lesions in a patient to undergo an endoscopic, intravascular catheter or surgical procedure, wherein the method comprises:

injecting the patient parenterally with a divalent single chain antibody fragment or subfragment with a molecular weight of 85,000 Daltons or less, specific to the lesion and which is labeled with a first labeling agent capable of detection using a detection device,

and with an indifferent protein from the same or different species as that used to prepare the specific fragment or subfragment, the indifferent protein being labeled with a second labeling agent capable of being independently detected using a detection device,

the labeling being so effected that the kinetics and distribution of the labeled specific protein and the labeled indifferent protein in the patient are substantially the same during the time period required for detection,

wherein at least one of the labeling agents is a photoactive dye;

and during the procedure detecting for presence of the labeling agents in the patient with the detection device, the level of activity of the labeled indifferent protein being used to determine the distribution of background activity due to non-targeted specific fragment or subfragment, whereby the activity of substantially only the targeted lesion-localized specific fragment or subfragment is determined and said lesion is thereby detected and localized.